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Antitubercular Evaluation of Isoxazolyl Chalcones.

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ABSTRACT

Fifteen chalcones have been synthesized by Claisen-Schmidt condensation reaction, purified and characterized by spectral and elemental analysis studies. MABA assay was employed to evaluate the antitubercular activity of the compounds. The compounds **3o** and **3l** exhibited comparable activity with that of the standard isoniazid. The structure activity relationships based on the results enabled to identify the essential structural feature for the activity.

Keywords: Claisen-Schmidt condensation, MABA assay, Antitubercular activity, Structure activity relationships.

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INTRODUCTION

Despite the advances in chemotherapy and the BCG vaccine, tuberculosis remains a major global threat. It is the second most prevalent infectious disease, next to HIV, in the world today than at any other time in human history. As per WHO - In 2012, an estimated 8.6 million people developed tuberculosis (TB) and 1.3 million died from the disease, including HIV positive individuals. The total resource requirement to combat TB and multi-drug-resistant TB (MDR-TB) is estimated to be US$ 4.8 billion each year over 2014-2016. The World Health Organization (WHO) and the Global Fund to Fight AIDS, TB and Malaria estimate that there is an annual anticipated demand for at least US$ 1.6 billion globally to bridge the funding gap over 2014- 2016, in 118 low and middle income countries which are eligible for financing from the Global Fund. Since 1995, 22 million lives were saved and 56 million people successfully cured and there is a 45% decrease in the TB mortality since 1990. In spite of these achievements 3 million people are estimated to be infected every year and there is an alarming burden of MDR-TB crisis [1].India is the highest TB burden country with World Health Organization (WHO) statistics for 2011 giving an estimated incidence of 2.2 million cases of TB for India out of a global incidence of 8.6 million cases. The estimated TB prevalence figure for 2011 is given as 3.1 million. It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB [2]. Hereafter there is an urgent need for the development of novel antitubercular agents to treat multidrug resistance tuberculosis which can act through a novel mechanism to combat MDR-TB.

Isoxazole ring is found in many of the clinically useful antimicrobials like sulfisoxazole, cloxacillin, dicloxacillin and the selective COX-2 inhibitor valdecoxib whereas its reduced form isoxazolidine ring forms the part of the antitubercular agent cycloserine [3-4]. Chalcones on the other hand possess broad spectrum of biological activities and are reviewed [5-9]. Hence in the present study we planned to synthesize and study the influence of novel chalcones containing isoxazole as ring-A portion and ring-B with pure methoxyl or a combination of methoxyl and halogen substituents for antitubercular activity.

MATERIALS AND METHODS

General

All the chemical reagents and solvents were purchased from Thermo Fisher Scientific Inc., Mumbai, India. 5-acetylisoxazole was purchased from local supplier. TLC using silica gel-G (Merck grade) as the adsorbent was used to monitor the reactions. Melting points were determined in open capillaries, using Boitus melting point apparatus, expressed in ^{o}C and are uncorrected. Bruker Vertex 80v spectrometer using potassium bromide disks was used to record the IR spectra. ^{1}H NMR spectra were recorded on Bruker AMX 400 MHz NMR spectrophotometer using TMS as an internal standard and the chemical shifts (δ) are expressed in ppm. Elemental analyses were carried out using a Carlo Erba 1108 elemental analyser for C, H, and N and the results are within ± 0.4% of the calculated values.

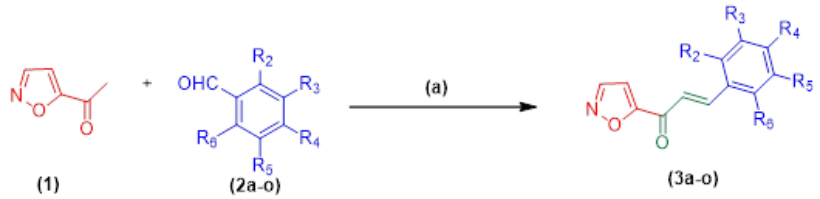
Chemistry

General method of synthesis of isoxazolylchalcones*:* The synthesis of the target compounds was performed using Claisen-Schmidt condensation reaction [10-11] and is presented in **Scheme 1**. The chalcones (**3a-o**) were prepared by reacting 1-(isoxazole-5-yl)ethanone(0.001 mole) with appropriate aromatic aldehyde (0.001 mole) in ethanol (7.5 mL) and an aqueous solution of KOH (10%, 7.5 mL) for 24 h at room temperature. The precipitate of the chalcone was then obtained by transferring the reaction mixture into crushed ice separately. The precipitate were filtered, washed thoroughly with water, dried and purified by recrystallized using either ethanol or chloroform as the solvents.

(*E*)-1-(isoxazole-5-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (3a): Yield 89%; **m.p.**186-188^{o}C; **IR** (KBr, cm^{-1}): 1652 (C=O), 1601 (C=C of Ar), 1511 (CH=CH), 1611 (C=N), 1128 (-OCH_3), 3058 (Ar C-H); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.74 (3H, s, Ar-OCH_3), 7.22 (1H, d, *J* = 17 Hz, -CO-CH=), 7.73 (1H, d, *J* =17 Hz, =CH-Ar), 6.01-8.22 (6H, Ar-H); **Anal. Calcd** for: $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11; Found: C, 68.21; H, 4.86; N, 6.26.

(*E*)-1-(isoxazole-5-yl)-3-(3-methoxyphenyl)prop-2-en-1-one (3b): Yield 81%; **m.p.**166-168^{o}C; **IR** (KBr, cm^{-1}): 1648 (C=O), 1600 (C=C of Ar), 1515 (CH=CH), 1618 (C=N), 1121 (-OCH_3), 3001 (Ar C-H); **^{1}H NMR** (400 MHz,

$CDCl_3$, ppm):δ 3.80 (3H, s, Ar-OCH_3), 7.18 (1H, d, *J* = 17 Hz, -CO-CH=), 7.68 (1H, d, *J* =17 Hz, =CH-Ar), 6.10-8.15 (6H, Ar-H); **Anal. Calcd** for: $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11; Found: C, 68.21; H, 4.86; N, 6.26.



3a: R_2=H; R_3=H; R_4=OCH_3; R_5=H; R_6=H
3b: R_2=H; R_3=OCH_3; R_4=H; R_5=H; R_6=H
3c: R_2=OCH_3; R_3=H; R_4=H; R_5=H; R_6=H
3d: R_2=OCH_3; R_3=OCH_3; R_4=H; R_5=H; R_6=H
3e: R_2=OCH_3; R_3=H; R_4=OCH_3; R_5=H; R_6=H
3f: R_2=OCH_3; R_3=H; R_4=H; R_5= OCH_3; R_6=H
3g: R_2=OCH_3; R_3=H; R_4=H; R_5=H; R_6=OCH_3
3h: R_2=H; R_3= OCH_3; R_4= OCH_3; R_5=H; R_6=H
3i: R_2=H; R_3= OCH_3; R_4=H; R_5=OCH_3; R_6=H
3j: R_2=OCH_3; R_3=OCH_3; R_4=OCH_3; R_5=H; R_6=H
3k: R_2=OCH_3; R_3=H; R_4=OCH_3; R_5= OCH_3; R_6=H
3l: R_2=OCH_3; R_3=H; R_4=OCH_3; R_5=H; R_6=OCH_3
3m: R_2=H; R_3= OCH_3; R_4=OCH_3; R_5=OCH_3; R_6=H
3n: R_2=F; R_3=OCH_3; R_4=OCH_3; R_5=H; R_6=H
3o: R_2=Cl; R_3=H; R_4=OCH_3; R_5=H; R_6=OCH_3

Scheme-1: Synthesis of isoxazolylchalcones (**3a-o**). Reagents and conditions: (**a**) ethanol, KOH, room temperature; (**1**) 1-(isoxazole-5-yl)ethanone (**2a-o**) Substituted aromatic aldehydes

(*E*)-1-(isoxazole-5-yl)-3-(2-methoxyphenyl)prop-2-en-1-one (3c): Yield 86%; **m.p.**177-179°C; **IR** (KBr, cm^{-1}): 1655 (C=O), 1606 (C=C of Ar), 1512 (CH=CH), 1609 (C=N), 1124 (-OCH_3), 3021 (Ar C-H); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.68 (3H, s, Ar-OCH_3), 7.23 (1H, d, *J* = 17 Hz, -CO-CH=), 7.70 (1H, d, *J* =17 Hz, =CH-Ar), 6.02-8.19 (6H, Ar-H); **Anal. Calcd** for: $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11; Found: C, 68.21; H, 4.86; N, 6.26.

(*E*)-1-(isoxazole -5-yl)-3-(2,3-dimethoxyphenyl)prop-2-en-1-one (3d): Yield74%; **m.p.** 201-203°C; **IR** (KBr, cm^{-1}): 1650 (C=O), 1608 (C=C of Ar), 1515 (CH=CH), 1611 (C=N), 1128 (-OCH_3), 3068 (Ar C-H);**^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.68 (3H, s, Ar-OCH_3), 3.70 (3H, s, Ar-OCH_3), 7.25 (1H, d, *J* = 17 Hz, -CO-CH=), 7.72 (1H, d, *J* =17 Hz, =CH-Ar), 6.02-8.19 (5H, Ar-H); **Anal. Calcd** for: $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.95; H, 5.22; N, 5.49.

(*E*)-1-(isoxazole-5-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3e): Yield88%; **m.p.** 146-148°C; **IR** (KBr, cm^{-1}): 1652 (C=O), 1610 (C=C of Ar), 1504 (CH=CH), 1622 (C=N), 1135 (-OCH_3), 2966 (Ar C-H);**^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.54 (3H, s, Ar-OCH_3), 3.75 (3H, s, Ar-OCH_3), 7.29 (1H, d, *J* = 17 Hz, -CO-CH=), 7.66 (1H, d, *J* =17 Hz, =CH-Ar), 6.05-8.14 (5H, Ar-H); **Anal. Calcd** for: $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.95; H, 5.22; N, 5.49.

(*E*)-1-(isoxazole-5-yl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (3f): Yield76%; **m.p.** 140-142°C; **IR** (KBr, cm^{-1}): 1656 (C=O), 1607 (C=C of Ar), 1501 (CH=CH), 1618 (C=N), 1131 (-OCH_3), 3064 (Ar C-H);**^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.64 (3H, s, Ar-OCH_3), 3.72 (3H, s, Ar-OCH_3), 7.21 (1H, d, *J* = 17 Hz, -CO-CH=), 7.71 (1H, d, *J* =17 Hz, =CH-Ar), 6.04-8.22 (5H, Ar-H); **Anal. Calcd** for: $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.95; H, 5.22; N, 5.49.

(*E*)-1-(isoxazole-5-yl)-3-(2,6-dimethoxyphenyl)prop-2-en-1-one (3g): Yield80%; **m.p.** 139-141°C; **IR** (KBr, cm^{-1}): 1649 (C=O), 1607 (C=C of Ar), 1508 (CH=CH), 1619 (C=N), 1133 (-OCH_3), 2995 (Ar C-H);**^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.58 (3H, s, Ar-OCH_3), 3.78 (3H, s, Ar-OCH_3), 7.20 (1H, d, *J* = 17 Hz, -CO-CH=), 7.73 (1H, d, *J* =17 Hz, =CH-Ar), 6.07-8.23 (5H, Ar-H); **Anal. Calcd** for: $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.95; H, 5.22; N, 5.49.

(*E*)-1-(isoxazole-5-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (3h): Yield75%; **m.p.** 181-183°C; **IR** (KBr, cm^{-1}): 1649 (C=O), 1602 (C=C of Ar), 1505 (CH=CH), 1620 (C=N), 1129 (-OCH_3), 3028 (Ar C-H);**^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.55 (3H, s, Ar-OCH_3), 3.80 (3H, s, Ar-OCH_3), 7.18 (1H, d, *J* = 17 Hz, -CO-CH=), 7.67 (1H, d, *J* =17 Hz, =CH-Ar), 6.12-8.12 (5H, Ar-H); **Anal. Calcd** for: $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.95; H, 5.22; N, 5.49.

(*E*)-1-(isoxazole-5-yl)-3-(3,5-dimethoxyphenyl)prop-2-en-1-one (3i): Yield81%; **m.p.** 112-114°C; **IR** (KBr, cm^{-1}): 1659 (C=O), 1610 (C=C of Ar), 1510 (CH=CH), 1621 (C=N), 1128 (-OCH_3), 3021 (Ar C-H);**^{1}H NMR** (400 MHz,

$CDCl_3$, ppm):δ 3.69 (3H, s, Ar-OCH_3), 3.84 (3H, s, Ar-OCH_3), 7.28 (1H, d, *J* = 17 Hz, -CO-CH=), 7.75 (1H, d, *J* =17 Hz, =CH-Ar), 6.11-8.21 (5H, Ar-H); **Anal. Calcd** for: $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 64.95; H, 5.22; N, 5.49.

(*E*)-1-(isoxazole-5-yl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (3j):Yield74%; **m.p.** 169-171°C; **IR** (KBr, cm^{-1}): 1655 (C=O), 1586 (C=C of Ar), 1511 (CH=CH), 1127 (-OCH_3); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.88 (3H, s, Ar-OCH_3), 3.92 (6H, s, 2x Ar-OCH_3), 7.25 (1H, d, *J* = 17 Hz, -CO-CH=), 7.55 (1H, d, *J* =17 Hz, =CH-Ar), 6.21-8.11 (4H, Ar-H); **Anal. Calcd** for: $C_{15}H_{15}NO_2$: C, 62.28; H, 5.23; N, 4.84; Found: C, 62.55; H, 5.44; N, 5.85.

(*E*)-1-(isoxazole-5-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (3k): Yield76%; **m.p.** 154-156°C; **IR** (KBr, cm^{-1}): 1652 (C=O), 1585 (C=C of Ar), 1498 (CH=CH), 1132 (-OCH_3); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.82 (3H, s, Ar-OCH_3), 3.90 (6H, s, 2x Ar-OCH_3), 7.21 (1H, d, *J* = 17 Hz, -CO-CH=), 7.52 (1H, d, *J* =17 Hz, =CH-Ar), 6.85-8.07 (4H, Ar-H); **Anal. Calcd** for: $C_{15}H_{15}NO_2$: C, 62.28; H, 5.23; N, 4.84; Found: C, 62.55; H, 5.44; N, 5.85.

(*E*)-1-(isoxazole-5-yl)-3-(2,4,6-triethoxyphenyl)prop-2-en-1-one (3l): Yield65%; **m.p.** 196-198°C; **IR** (KBr, cm^{-1}): 1658 (C=O), 1578 (C=C of Ar), 1521 (CH=CH), 1133 (-OCH_3); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.85 (3H, s, Ar-OCH_3), 3.91 (6H, s, 2x Ar-OCH_3), 7.29 (1H, d, *J* = 17 Hz, -CO-CH=), 7.68 (1H, d, *J* =17 Hz, =CH-Ar), 6.25-8.28 (4H, Ar-H); **Anal. Calcd** for: $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; Found: C, 62.55; H, 5.44; N, 5.85.

(*E*)-1-(isoxazole-5-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (3m): Yield88%; **m.p.** 222-224°C; **IR** (KBr, cm^{-1}): 1661 (C=O), 1578 (C=C of Ar), 1522 (CH=CH), 1125 (-OCH_3), 3102 (Ar C-H); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.85 (3H, s, Ar-OCH_3), 3.86 (6H, s, 2x Ar-OCH_3), 7.19 (1H, d, *J* = 17 Hz, -CO-CH=), 7.66 (1H, d, *J* =17 Hz, =CH-Ar), 6.01-8.22 (4H, Ar-H); **Anal. Calcd** for: $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; Found: C, 62.55; H, 5.44; N, 5.85.

(*E*)-1-(isoxazole-5-yl)-3-(2-fluoro-3,4-dimethoxyphenyl)prop-2-en-1-one (3n): Yield91%; **m.p.** 272-274°C; **IR** (KBr, cm^{-1}): 1659 (C=O), 1580 (C=C of Ar), 1524 (CH=CH), 1121 (-OCH_3), 935 (C-F), 3102 (Ar C-H); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.64 (3H, s, Ar-OCH_3), 3.83 (3H, s, 2x Ar-OCH_3), 7.25 (1H, d, *J* = 17 Hz, -CO-CH=), 7.71 (1H, d, *J* =17 Hz, =CH-Ar), 6.51-8.25 (4H, Ar-H); **Anal. Calcd** for: $C_{14}H_{12}FNO_4$: C, 60.65; H, 4.36; N, 5.05; Found: C, 61.21; H, 5.01; N, 5.64.

(*E*)-1-(isoxazole-5-yl)-3-(2-chloro-4,6-dimethoxyphenyl)prop-2-en-1-one (3o): Yield87%; **m.p.** 248-250°C; **IR** (KBr, cm^{-1}): 1663 (C=O), 1576 (C=C of Ar), 1521 (CH=CH), 1119 (-OCH_3), 895 (C-F), 3110 (Ar C-H); **^{1}H NMR** (400 MHz, $CDCl_3$, ppm):δ 3.56 (3H, s, Ar-OCH_3), 3.81 (3H, s, 2x Ar-OCH_3), 7.23 (1H, d, *J* = 17 Hz, -CO-CH=), 7.62 (1H, d, *J* =17 Hz, =CH-Ar), 6.45-8.20 (4H, Ar-H); **Anal. Calcd** for: $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77; Found: C, 58.01; H, 4.32; N, 4.91.

In-Vitro Antitubercular Activity

The preliminary antitubercular screening for test compounds was obtained for *M. tuberculosis* $H_{37}Rv$, the MIC of each compound was determined by broth dilution assay [12-14] and is defined as the lowest concentration of drug, which inhibits ≤ 99% of bacterial population present at the beginning of the assay. A frozen culture in Middlebrook 7H9 broth supplemented with 10% albumin-dextrose-catalase and 0.2% glycerol was thawed and diluted in broth to 10^5 cfu mL^{-1} (colony forming unit/mL) dilutions. Each test compound was dissolved in DMSO and then diluted in broth twice at the desired concentration. The final concentration of DMSO in the assay medium was 1.3%. Each U-tube was then inoculated with 0.05 mL of standardized culture and then incubated at 37°C for 21 days. The growth in the U-tubes was compared with visibility against positive control (without drug), negative control (without drug and inoculum) and with standard isoniazid.

RESULTS AND DISCUSSIONS

Chemistry

The novel isoxazolylchalcones were synthesized by base-catalysed Claisen-Schmidt condensation of 1-(733soxazole-5-yl)ethanone with different methoxylated aromatic aldehydes as illustrated in **Scheme 1**. Impure compounds were purified by recrystallization using chloroform. Spectroscopic data (IR and ^{1}H NMR) of the pure compounds was utilized to elucidate the structures of the compounds and the results were consistent

with the proposed structures. The characteristic IR absorption bands in the range 1648-1661 cm^{-1} (-C=O) and 1498-1522 cm^{-1} (-C=C-) respectively confirmed the structure of chalcone bridge. Additional –C=C- and –C-H stretching bands in the range 1578-1610 cm^{-1} and 3010-3150 cm^{-1} had confirmed the presence of aromatic rings. The ^{1}H NMR spectrum of these compounds showed the characteristic resonance of –CO-CH= (*α*-H) around *δ* 6.7-7.4 ppm and *δ* 7.3-7.8 =CH-Ar (*β*-H) as doublets with coupling constant (*J* =17 Hz) respectively confirming the *trans* geometry at the ethylenic double bond of the molecule. The peaks between chemical shift 6-8.5 accounts for the other aromatic protons. Other protons exhibited additional resonance signals typically present in each compound. The composition of the synthesized compounds was confirmed by elemental analysis and the results were within ± 0.4 % of the calculated values.

Antitubercular activity and SAR

The antitubercular evaluation of the synthesize compounds was carried out using MABA assay. The results of the activity are presented in Table 1 and Figure 1. The compounds **3o** and **3l** exhibited excellent activity with MIC values 1 and 2µg/mL respectively whereas the compounds **3i** and **3b** are the least in potency. Other compounds exhibited considerable activity with an MIC in the range 8 to 62.5 µg/mL.

Table 1: Preliminary antitubercular activity of the synthesized compounds (3a-3o)

Compound	MIC values (µg/mL) of *M. tuberculosis* $H_{37}Rv$
3a	62.5
3b	512
3c	126
3d	62.5
3e	16
3f	62.5
3g	16
3h	126
3i	252
3j	16
3k	16
3l	2
3m	32
3n	2
3o	1
Isoniazid	0.25

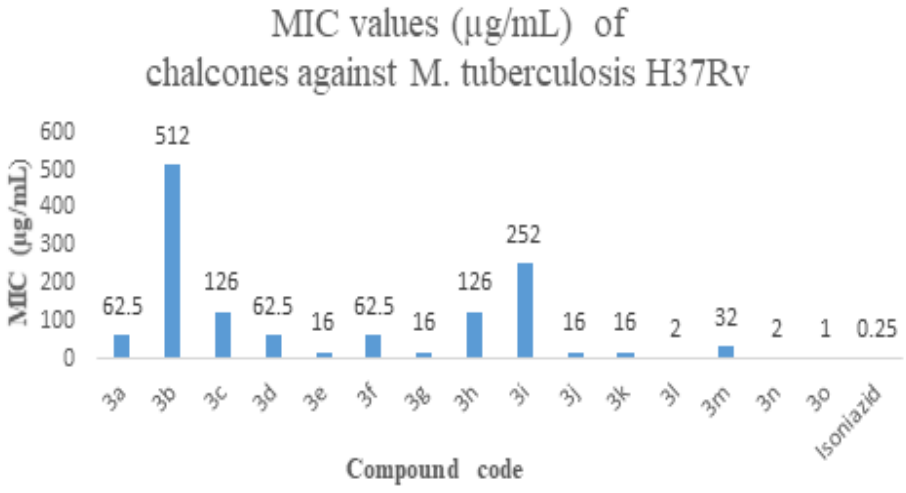


Figure 1: Graphical representation of antitubercular activity of 3a-3o against *M. tuberculosis* $H_{37}R$

Structure-Activity-Relationship study based on the above results indicated that the isoxazole ring with chalcone bridge is essential for the activity as well as both electron donating methoxyl group as well as electron withdrawing halogens like chlorine or fluorine groups on ring-B for the activity. Both the number and position of the substituents on the ring-B of chalcones influenced the activity. More is the number of the substituents grater will be the activity provided if the substituents are in the correct positions. The chalcones, **3o** and **3l** containing *ortho* and *para* substitutions are most active in the series whereas **3b** containing single methoxyl group at the *meta* position is the least active. However chalcone **3n** containing a 3,4-dimethoxy with ortho-fluorine substituents is more potent than the compounds with three methoxyl groups in the ortho and meta positions. Hence the combination of both methoxyl and halogen substituents has greater effect on the activity than presence of only methoxyl substituents. For example among the 2,4,6-trisubstituted compounds in the series **3o** containing both type of substituents was more active than **3l** containing only methoxyl groups.

CONCLUSIONS

In conclusion we synthesized 15 chalcones and evaluated for antitubercular activity using MABA assay. These results gives an insight into the SAR features required for the antitubercular activity suggesting that the presence of both methoxyl and halogen substituents on ring-B at positions-2,4,6 are essential. Further studies need to be carried out in order to diagnose the mode of action and molecular interaction of these chalcones with target to enhance the potency of these compounds.

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